

**REMARKS**

**I. Status of the Application**

Applicants thank Examiner Schnizer for withdrawing the finality of the previous Office Action, and hereby request a refund of the unnecessary extension of time and notice of appeal fees paid while Applicants were awaiting the issuance of the instant Office Action. Applicants also thank the Examiner for returning initialed Information Disclosure Statements and for withdrawing several previous claim rejections.

Claims 1-26 are currently pending. The Office withdrew claims 3, 6, and 7 due to an election of species requirement, but is now examining claim 6. (Office Action at page 2.) Applicants again request rejoinder of the withdrawn claims once the Office finds claims 1-2, 4-6, and 8-26 allowable.

Applicants amend claim 1 and claim 8 to recite that "the attachment between the aryl radical and the molecule to be transported is stable *in vivo*." This amendment is supported throughout the application as a whole, for example, at page 6, lines 1-19, page 23, lines 11-16, and in original claim 17. It does not introduce new matter.

Applicants amend claim 9 to make it independent of claim 1 and claim 8, and amend claims 11, 16, 17, 22, and 24-26 to depend from claim 1, claim 8, or claim 9, rather than from only claim 1 or claim 8. Applicants also include the radical F10 in claim 9. F10 is presented, along with F1-9 and F11, in Figures 1 and 2(a-b). These changes do not introduce new matter and are supported by the application as a whole.

Applicants rephrase claim 7 to correspond with a previous amendment of claim 6, which removed the phrase "low-molecular weight compound" from that claim.

Applicants also rephrase claims 11 and 22 to correspond with a previous amendment of

claim 12, which replaced the phrase "reactive function" with "reactive group." Finally, Applicants remove a redundant phrase from claim 10 and replace the British spelling of "tumour" in claim 21 with the corresponding American spelling "tumor." These changes are supported by the application as a whole, do not introduce new matter, and are merely intended to improve the format of the claims.

Applicants respectfully request the entry of all of these amendments.

## **II. Claim 11 Is Free From Objection**

The Office objects to claim 11 because it recites "reactive function group" while claim 12 was previously amended to recite "reactive group." (Office Action at page 3.) Applicants herein amend claim 11, as well as claim 22, to correspond with claim 12. Thus, Applicants request the withdrawal of this objection.

## **III. Claim 9 Is Definite**

The Office rejects claim 9 under 35 U.S.C. § 112, second paragraph, asserting that it is indefinite in light of a prior amendment of claim 1 that lengthened the R<sub>1</sub> substituent in formula I. (*Id.*) Applicants herein make claim 9 independent, rendering this rejection moot. Hence, Applicants request the withdrawal of this rejection.

## **IV. Claims 1-2, 4-6, and 10-26 Are Supported by the Application**

The Office rejects claims 1-2, 4-6, and 10-26 under 35 U.S.C. § 112, first paragraph, as allegedly not supported by the application. (Office Action at pages 4-7.) Applicants traverse this rejection.

The Office contends that the genus of claim 1 encompasses conjugates similar to those of "Iyer 1997" (Iyer et al., *Bioorg. Med. Chem.*, 7(7): 871-6 (1997)), and contends

that Iyer's conjugates do not share the same advantageous properties as Applicants' conjugates. (Office Action at pages 4-5.) This rejection is moot because claim 1 now recites that "the attachment between the aryl radical and the molecule to be transported is stable *in vivo*."

As the instant application points out, the compounds of Iyer 1997 are all bioreversible prodrugs. (Specification at page 6, lines 1-19.) For example, Iyer's paper discloses "bioreversible prodrug conjugates" that undergo "esterase-mediated conversion" to release a free oligonucleotide *in vivo*. (See Iyer 1997 at the paragraph bridging pages 871 and 872, and Figures 1 and 2.) Thus, Iyer et al. designed their oligonucleotide conjugates so that esterase enzymes would specifically disassemble them *in vivo*. (Iyer at page 871, first paragraph.) In contrast, in Applicants' conjugates, the covalent bond between the aryl radical and the molecule to be transported is preserved during uptake into the cell. (Specification at page 6, lines 11-19.) In further contrast to Iyer 1997, the instant claimed conjugates enhance the uptake of the molecule to be transported into cells and improve its distribution within the cell. (*Id.*)

The Office also contends that the application's disclosure only supports the thioamide or carbonyl attachments recited in claim 8 because the application allegedly does not specifically list other possible groups or show actual reduction to practice of the invention using other groups. (Office Action at pages 5-6.) It is a basic tenet of patent law that actual reduction to practice is not a patentability requirement. M.P.E.P. §§ 2163 and 2164.02; *and see Gould v. Quigg*, 3 U.S.P.Q.2d 1302, 1304 (Fed. Cir. 1987). Further, literal support, such as by listing particular linkages, is also not required to satisfy 35 U.S.C. § 112. M.P.E.P. § 2163.02. Indeed, patent applications are not

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meant to be blueprints. Instead, they should exclude material that is known in the art. M.P.E.P. § 2164.01. In this case, one of ordinary skill in the art, using his knowledge of chemistry and the available literature, can readily select appropriate stable attachments between the claimed aryl radicals and the molecules to be transported. Thus, Applicants do not need to provide a list of all possible linkages in order to demonstrate possession of the invention. In fact, the Office itself contends elsewhere in this Office Action that “the prior art teaches that the use of linkers is routine in the art . . . and the selection of a particular linker is a matter of design choice,” and cites patents by Choi et al. and Norden et al. in support of this statement. (Office Action at page 17, first full paragraph.)

Further, this rejection is based upon the original language of claim 1 and not upon any later amendments. The M.P.E.P. specifically counsels that written description rejections based upon original claims “should be rare” because there is a strong presumption that the application supports them. M.P.E.P. § 2163.03.

Finally, in making this rejection, the Office focuses on the wording at page 5, lines 21-34, that advantageous properties may apply to conjugates “of a certain structure.” The Office asserts that Applicants fail to adequately describe that “certain structure.” (Office Action at pages 4-5.) However, the Office takes this phrase out of context. This phrase occurs at an early part of the application, and serves in part as introduction to a further description of the claimed conjugate structures that immediately follows in the “summary of the invention” section of the text and continues elsewhere in the application and figures.

For all of these reasons, Applicants claims are fully supported by the application, and Applicants request the withdrawal of this rejection.

**IV. Claims 1, 6, 11-12, and 16-26 Are Novel**

The Office asserts that claims 1, 6, 11-12, and 16-26 are anticipated by "Lucas" (Lucas et al., U.S. Patent No. 5,698,411). (Office Action at pages 7-8.) Applicants traverse this rejection.

Claim 1 and its dependents require that the attachment between the aryl radical and the molecule to be transported is stable *in vivo*. In contrast, Lucas's fluorescent conjugates are specifically designed to be disassembled by enzymes *in vivo* in order to act as reporters of enzyme activity. Lucas attaches a fluorescent compound (indicator group) to an enzyme substrate (leaving group) such that the fluorescence is quenched. (See Lucas at col. 2, lines 30-47, and at cols. 7-10.) When an enzyme cleaves the conjugated substrate *in vivo*, the fluorescent compound is released, so that its signal can be observed. This fluorescent signal allows a researcher to monitor the *in vivo* activity of a cleavage enzyme. Lucas's invention would be inoperable if the attachment between its fluorescent compound and enzyme substrate was stable *in vivo*. Because Lucas requires a bioreversible linkage, it cannot anticipate any of claims 1, 6, 11-12, and 16-26.

Further, even if, *arguendo*, Lucas did not require such a bioreversible linkage, it still could not anticipate any of claims 1, 6, 11-12, and 16-26. For example, the Office asserts that Applicants' claimed genus is encompassed within Lucas's disclosure at the paragraph bridging columns 9 and 10, and at column 23, lines 43-65. Here, Lucas discloses that one could attach "amino acids, peptides, saccharides, sulfates,

phosphates, esters, phosphate esters, nucleotides, polynucleotides, nucleic acids, pyrimidines, purines, nucleosides, lipids, and mixtures thereof" to one of its fluorescent compounds, and comments that one could also attach two different substituents such as a peptide and a lipid. Lucas also provides a six page table of possible substituents with about 120 different entries. (See Lucas at cols. 9-21.) In other words, one could choose from many large classes of biologically important molecules or functional groups, with different chemical and structural properties.

In order for such a broad, generic disclosure to anticipate a specific genus such as Applicants claim, one of ordinary skill in the art must be able to clearly envision the claimed genus within the reference's broad disclosure. See, e.g., *In re Ruchig*, 145 U.S.P.Q. 274, 282 (C.C.P.A. 1965). Lucas fails this test because Lucas discloses a nearly infinite array of aryl group substituents with different structures and chemical properties such as charge and polarity. One of ordinary skill in the art reading Lucas would not clearly envision the genus with the structural requirements of X, Y, R<sup>1</sup>, and R<sup>2</sup> that Applicants claim. Instead, bridging the gap between Lucas's vast range of possibilities to the discreet X, Y, R<sup>1</sup>, and R<sup>2</sup> groups of claim 1 would require a number of conscious design choices.

For these reasons, Applicants respectfully request the withdrawal of this rejection.

#### **V. All of the Claims Are Nonobvious**

There are three distinct requirements for a *prima facie* case of obviousness.

First, the references must teach or suggest every claim element. M.P.E.P. §§ 2142 and 2143.03. Second, there must be a motivation to modify or combine the teachings of the

cited references. M.P.E.P. §§ 2143 and 2143.01. Third, there must be a reasonable expectation of success in performing the modified or combined teachings of the references. M.P.E.P. § 2143.02.

The motivation to combine or modify references and the reasonable expectation of success must come from the references themselves or from the knowledge generally available to one of ordinary skill in the art, and not by hindsight from the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2142. Further, the mere fact that the references *can* be combined or modified does not itself render the combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The modification or combination must be *desirable*, not merely feasible. M.P.E.P. § 2143.01; *Winner v. Wang*, 53 U.S.P.Q.2d 1580, 1587-8 (Fed. Cir. 2000).

Each of the rejections below fails this three-part test. Thus, Applicants request the withdrawal of each rejection.

**1. Rejection of Claims 1-2, 4-6, 10, and 22-26 over Publications by Iyer et al.**

The Office contends that claims 1-2, 4-6, 10, and 22-26 are obvious over Iyer 1997, discussed above, in view of two other publications by Iyer et al., "Iyer 1996" (Iyer et al., *Bioorg. Med. Chem.* 6(16): 1917-22 (1996)) and "Iyer 1994" (Iyer et al., *Bioorg. Med. Chem.* 4(20): 2471-76 (1994)). (Office Action at pages 8-9.) Applicants traverse this rejection.

The Office contends that Iyer 1997 discloses a conjugate that differs from a particular species of claim 1 only by a methyl group. There is another fundamental difference between Iyer 1997 and claim 1, however. Claim 1 requires that the attachment between the aryl radical and the molecule to be transported is stable *in vivo*.



In contrast, Iyer 1997 discloses only bioreversible linkages specifically cleaved *in vivo* by esterase enzymes.<sup>1</sup> (See Iyer 1997 at pages 871-872 and Figures 1-2.)

In fact, all three Iyer publications focus entirely upon bioreversible, prodrug conjugates cleaved *in vivo* by esterases. Iyer 1994 investigates the stereochemistry of the esterase cleavage of oligonucleotide prodrugs using serum and liver esterases. (See Iyer 1994 at page 2471, and Tables 1-3, for example.) Iyer 1996 describes acycloxyaryl prodrugs of oligonucleotide phosphorothioates and includes a figure showing how they are cleaved by esterases *in vivo*. (Iyer 1996 at page 1917 and Figure 1.) Iyer 1997 provides further discussion of bioreversible acycloxyaryl prodrugs and their hydrolysis by esterases. Iyer 1997 also comments that delivering oligonucleotides as reversible prodrugs is beneficial because "conjugation with a ligand might compromise the antisense potential of an oligonucleotide." (Iyer 1997 at page 871, first paragraph.) Accordingly, according to Iyer 1997, bioreversibility restores the "natural affinity and selectivity of the antisense oligonucleotide for the target . . . without interference from the conjugating ligand." (*Id.*)

None of the Iyer publications would motivate one of ordinary skill in the art to make the instant, claimed conjugates. In fact, one of ordinary skill in the art making the instant conjugates proceeds contrary to Iyer's advice to build an esterase-cleavable linkage between the molecule to be transported and the conjugating compound. Thus, Iyer's publications as a whole teach away from the compounds of claim 1. Such teaching away is "strong evidence of unobviousness." *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983).

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<sup>1</sup> While the Office also cites Iyer 1996 and Iyer 1994, it makes no specific remarks about them in relation to claim 1.



Because the three Iyer publications teach away from Applicants' claim 1, they provide no motivation for one of ordinary skill in the art to make the conjugates or perform the processes of claims 2, 4-6, 10, and 22-26. Thus, Applicants' claims are unobvious over Iyer 1994, 1996, and 1997.

**2. Rejection of Claims 16-19 over the Iyer Publications in view of Yamamoto et al. or White et al.**

The Office also asserts that claims 16-19 are obvious over Iyer 1997, Iyer 1996, and Iyer 1994, as well as publications by "Yamamoto" (Yamamoto et al., *Genetics* 131(4): 811-19 (1992)) and "White" (White et al., *Antimicrob. Agents and Chemother.* 41(12): 2699-2704 (1997)). (Office Action at pages 10-11).

Applicants traverse this rejection for the reasons above. The three Iyer publications do not render claim 1 obvious because they teach only bioreversible conjugates. The Office cites Yamamoto and White merely for the notion of delivering antisense oligonucleotides to yeast and *E. coli* cells. There is nothing in either Yamamoto or White that suggests using a stable conjugate according to Applicants' claim 1. Thus, this combination of publications does not render claims 16-19 obvious because there is no motivation to combine or modify them.

**3. Rejection of Claims 16-21 Over the Iyer Publications and Higgins et al.**

The Office further rejects claims 16-21 over the three Iyer publications discussed above as well as over Higgins et al. (*Proc. Natl. Acad. Sci.* 90: 9901-5 (1993)). (Office Action at pages 11-12). Applicants traverse this rejection for the same reasons discussed in sections 1 and 2 above.

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Again, the three Iyer publications disclose only bioreversible conjugates. The Office relies on Higgins et al. for the notion of delivering oligonucleotides to tumor cells. There is nothing in Higgins to suggest administering a stable conjugate as Applicants claim. Thus, this combination of publications does not render claims 16-21 obvious because there is no motivation to combine or modify them.

#### **4. Rejection of Claims 11, 13, and 14 over Lucas**

The Office asserts that claims 11, 13, and 14 are obvious over Lucas, based on the anticipation rejection of claim 1 discussed previously. (Office Action at pages 12-13.) Applicants traverse this rejection because, like the Iyer articles, Lucas describes only bioreversible conjugates.

Like Iyer, Lucas's intent is to design enzymatically bioreversible conjugates. (See section IV above.) Further, because Lucas uses these conjugates to monitor the activity of the enzymes that cleave them, Lucas's conjugates would be inoperative if they were not bioreversible. Therefore, modifying Lucas's teachings to obtain The invention of Applicants' claim 1 and its dependents would render Lucas inoperable for its intended purpose. Such a reference cannot be used to support an obviousness rejection. See M.P.E.P. § 2143.01; and see *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 n. 12 (Fed. Cir. 1992); *In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1985); *In re Ratti*, 123 U.S.P.Q. 349, 352 (C.C.P.A. 1959). Thus, Lucas cannot render claims 11, 13, or 14 obvious.

Even if, *arguendo*, Lucas could be operatively modified, Lucas cannot support this rejection because Lucas discloses a nearly infinite array of substituents for its fluorescent aryls, as discussed previously. The only way one of ordinary skill in the art

could arrive at Applicants' selection of X, Y, and R<sup>1</sup> groups from this nearly limitless range of possibilities is by consciously picking and choosing those particular substituent groups, and also by adding a further substituent to represent Applicants' "molecule to be transported."

The many conscious choices necessary to go from Lucas's substituents to the claimed X, Y, and R<sup>1</sup> illustrate that this rejection is based on impermissible hindsight rather than on any real motivation to modify Lucas. As the Federal Circuit points out, the Office cannot use the application as a "guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims." *Grain Processing Corp. v. American Maize-Prods. Co.*, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988).

For these reasons, Lucas does not render claims 11, 13, and 14 obvious.

**5. Rejection of Claims 1-2, 4-5, 10-12, and 15-26 over Lucas in View of Pitt et al.**

The Office also rejects claims 1-2, 4-5, 10-12, and 15-26 over Lucas in view of the abstract of "Pitt." (Pitt et al., *J. Gen. Microbiol.* 56(3): 321-9 (1969)). (Office Action at pages 13-14.) Applicants traverse this rejection for the same reasons discussed above with respect to claims 11, 13, and 14.

Further, the Office relies on Pitt for the idea that oligonucleotides are substrates for enzymes that Lucas's assay could monitor, and contends that Lucas could be modified to measure the activity of those enzymes. (Office Action at page 14.) However, if one of ordinary skill were to modify Lucas in this way, he would obtain a bioreversible conjugate rather than a stable conjugate of claim 1. There is no other

disclosure in Pitt that would provide motivation to make a stable conjugate because Pitt does not relate to delivery of macromolecules across cell membranes. Instead, Pitt discloses that microbes release various cleavage enzymes such as esterases, proteases, and RNase when they infect plant tissue. Thus, Lucas and Pitt cannot render any of claims 1-2, 4-5, 10-12, and 15-26 obvious.

**6. Rejection of Claims 8, 11-14, and 16-26 over Lucas in View of Choi et al. or Norden et al. and Rejection of Claims 8, 10-12, and 15-26 over Lucas in View of Pitt et al. and Either Choi et al. or Norden et al.**

Finally, the Office rejects claim 8 and several of its dependents over Lucas in view of "Choi" (U.S. Patent No. 5,820,873) or "Norden" (U.S. Patent No. 6,228,982 B1), or over Lucas in view of Pitt and either Choi or Norden. (Office Action at pages 15-17.) Applicants also traverse these rejections for the same reasons given above.

Like claim 1, claim 8 recites that the attachment between the aryl radical and the molecule to be transported is stable *in vivo*. Thus, applying Lucas to claim 8 renders Lucas inoperable for its intended purpose. As discussed above, a reference cannot be used in an obviousness rejection if modifying it would destroy its intended purpose.

Further, Lucas presents a vast array of different substituents that one of ordinary skill in the art must consciously wade through in order to arrive at an aryl group substituted with the claimed X, Y, and R<sup>1</sup> groups and a "molecule to be transported." In addition to the X, Y, and R<sup>1</sup> groups of claim 1, claim 8 requires an R<sup>3</sup> group that may be a carbonyl or thioamide.

The Office contends that Choi and Norden suggest the carbonyl or thioamide. However, Choi, Norden, and Lucas do not lead one of ordinary skill in the art to the genus of claim 8. For example, the Office cites Choi at col. 5, line 50, to col. 6, line 7,

for the proposition that it is routine to join two molecules through a linker group and that the linker group could be a carbonyl. This paragraph of Choi, however, recites a large number of different linking functionalities, including “amido, amine, ether, ester, thioether, carboxyl, carbamate, carbonyl, carbonate, urea, or phosphoro.” Given this large list, Choi provides no motivation to select a carbonyl as Applicants do. Moreover, Choi does not mention a thioamide group. The Office cites Norden at col. 2, lines 18-22. Norden here recites a linking moiety of an “amide, thioamide, sulfinamide, or sulfonamide” but does not mention a carbonyl.

Together, Choi and Norden present a list of 14 different linkers with a variety of different structures and charges, some cleavable by esterases, some not. These two lists of possibilities, in combination with the vast array of substituents in Lucas, do not guide one of ordinary skill in the art to the genus of Applicants’ claim 8. For example, neither Choi nor Norden limits the number of conscious choices one of ordinary skill in the art would be required to make in order to bridge the gap between Lucas and the genus of claim 8. Moreover, neither Choi or Norden is concerned with the issue Applicants’ faced. Instead, Choi relates to liposomes while Norden relates to making peptide-nucleic acids.

Given the deficiencies of these three patents, it is again apparent that the Office has impermissibly used the instant application as a blueprint from which to construct combinations of prior art by hindsight. Thus, the Office has not satisfied its burden to present a *prima facie* case of obviousness. Indeed, the Federal Circuit repeatedly states that to make a *prima facie* case, “particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have

selected *these components in the manner claimed*" (emphasis added). *In re Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002), quoting *In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). Thus, the Office must do more than cite references that happen to mention the instant linkers in the context of a vast array of possibilities. The Office must present substantial evidence that one of ordinary skill in the art would desire to make an alkyl radical of the formula I linked to a "molecule to be transported" via the R<sup>3</sup> groups that Applicants claim.

Finally, Pitt does not relate to delivery of macromolecules across cell membranes but merely discloses a few known cellular cleavage enzymes. Therefore, nothing in Pitt would motivate one of ordinary skill in the art to make Applicants' claimed conjugates.

Because these combinations of references provide no motivation for one of ordinary skill in the art to make the conjugates of claim 8, they do not render claim 8 or its dependents obvious.

### CONCLUSION

Applicants submit that this application is in condition for allowance.

Please grant any extensions of time required to enter this response and charge any required fees not found herewith to Deposit Account No. 06-0916.

Respectfully submitted,

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